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The morbidity of malaria: a strategy for seafarer safety

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Malaria is one of the world's deadliest diseases and one of the world's leading causes of sickness and death. The disease causes more morbidity than mortality in adults and has a propensity for clinical relapse and recurrence. According to the World Health Organization, the estimated annual global incidence of malaria is 300 to 500 million cases of malaria with ca. 1.5 to 2.7 million deaths, mostly in infants, children, and pregnant women. Although typically an illness of tropical regions of the world, more cases (nearly all foreign-originating) are diagnosed in temperate countries each year. With its global grip and the concomitant increase in travellers, trade, and business, malaria has also now become a global occupational disease, especially in seafarers. By the nature of their job they cannot avoid malarial regions and generally suffer from a lack of medical help aboard, insufficient knowledge of preventive measures, and lack of up-to-date information about chloroquine-resistant areas. Malaria is listed as one of the leading causes of fever resulting from travel to tropical or subtropical countries. This article outlines a strategy to assist in formulating a protocol for prophylaxis aimed at prevention and immediate treatment in seafarers.

Sub-Saharan Africa is the region with the highest malaria infection rate. Here alone, the disease kills at least one million people each year. According to some estimates, 275 million out of a total of 530 million people have malaria parasites in their blood, although they may not develop symptoms [5, 6]. In the early 1960s, only 10% the world's population was at risk of contracting malaria. This rose to 40% as mosquitoes developed resistance to pesticides and malaria parasites developed resistance to treatment drugs [5]. According to material from Third World Network Features, in Africa alone, direct and indirect costs of malaria amounted to US $800 million in 1987 and are expected to reach US $1.8 billion annually by 1995 [4, 2]. The economic and human costs Involved in dealing with an outbreak of malaria on a ship that has just left the West African Coast [1] (Figure 1), are huge as the disease can cause loss of life and severe incapacitation as well as loss of crew members both from incapacity and from the care needs of those who are unwell. Diversion to obtain medical care or evacuation of ill crew members may also be needed. Malaria is now spreading to areas previously free of the disease. Actually, malaria transmission occurs in more than 100 countries throughout Africa, Asia, Latin America, and on certain Caribbean and Pacific islands. Malaria is presently endemic in most countries around the equator, in areas of Central and South America, many parts of Asia, especially in South East Asia, and most areas of sub-Saharan Africa, where up to 90% of all malaria fatalities occur. The geographic distribution of malaria is complex, and malaria-free or malaria--afflicted zones are very close to each other. Malaria is much more common in rural areas than in cities in most malaria zones, but, for instance, in Africa the high risk exists in cities too. If the prevalence of malaria stays on its present level, the estimated death rate could even double in the next 20 years.

Malaria is an acute or chronic disease- preventable, life-threatening disease transmitted by the bite of the female Anopheles mosquito. Among more than 100 species of plasmodia there are five types of malaria that affect humans: *Plasmodium falciparum* (which is responsible for the vast majority of malaria deaths), *Plasmodium vivax*, *Plasmodium ovale, Plasmodium malariae*, and *Plasmodium knowlesi.*

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Figure 1. Malaria's global grip. Between 300 million and 500 million acute cases of malaria are reported each year — 9 out of 10 of them occur in sub-Saharan Africa. Dark: current malaria transmission. Grey: malaria largely eliminated. White: malaria not present

MALARIA ENDEMICITY

Holoendemic malaria occurs when transmission is all year long: hyperendemic — transmission intense, but with periods of no transmission during the dry season; mesoendemic — regular seasonal transmission (unstable malaria); and hypoendemic — when very intermitted transmission occurs. Stable *P. falciparum* malaria occurs in holoendemic and hyperendemic areas; anaemia and high childhood mortality is seen. Adults living in these areas show some resistance, and many of them are asymptomatic. For unstable malaria many adult symptomatic cases are typical and high risk of fatalities occurs. In these areas there are seasonal and periodic epidemics. In most of sub-Saharan African countries there is mainly holo- and mesoendemic malaria [4, 9].

Malaria infection is not a risk at sea or on offshore oil terminus facilities that are distant from shore, provided that no female *Anopheles* mosquitoes have boarded the vessel or laid their eggs there. However, docking in many ports may place crew members at risk, whatever their background or previous exposure, particularly if they go ashore [3, 10, 12, 13]. Similarly, transits through infected areas when joining ships or whilst on leave may give rise to cases onboard. Immunity to malaria is not lifelong and so even those who had immunity from past exposure will very likely lose it and become vulnerable to reinfection with severe consequences after a period at sea or in non-malarial areas. There are several different strains of malaria, and exposure to one does not protect against the others. Falciparum malaria can be rapidly life threatening. It is common in many areas of the tropics, and an especially high level of precaution is needed to prevent exposure in locations where it is present. The clinical picture of the disease is highly variable but is generally characterized by periodic paroxysms of fever and chills, anaemia, and splenomegaly. Any fever must be observed with suspicion and the test, if a kit is available on board, must be carried out immediately. Rapid diagnosis is made by immunochromatographic test that detects malaria antigens (sensitivity 90–95%, specificity 72–92%). In case the kit is unavailable, treatment on suspicion is justifiable. Nevertheless, final microscopic diagnosis is necessary in a professional lab.

Symptoms appear seven days or more (usually 10–15 days) after the infective mosquito bite. The first symptoms — fever, headache, chills, and vomiting — may be mild and difficult to recognize as malaria. If not treated within 24 hours, *P. falciparum* malaria can progress to severe illness often leading to death. Children in endemic areas with severe disease frequently develop one or more of the following syndromic presentations: severe anaemia, respirato-

ry distress in relation to metabolic acidosis, or cerebral malaria. In adults, including seafarers, multi-organ involvement is also frequent.

VACCINES

The French scientist Laveran may have discovered the malarial parasite plasmodium way back in 1880; however, a vaccine against malaria is still far off. There is a global need for this vaccine and intense research is in progress to make the same available. There are several vaccine development projects in progress worldwide [2] and it may well be another 5 to 7 years before the vaccine will reach markets. Infants and children living in malaria endemic areas will be the first target group for the vaccine. Seafarers, travellers, and those living in malaria endemic areas will be the next target group to whom the vaccine will be made available. However, it has to be understood that the vaccine, when available, will only form part of a malaria preventive strategy.

In India, scientists like Chetan Chitnis from the International Centre for Genetic Engineering and Biotechnology (ICGEB) [7] at New Delhi, along with his team, are trying hard to make the vaccine reach the phase I trial as soon as possible. Working with Plasmodium, the malarial parasite, is difficult as the organism undergoes fast mutations and the vaccine has to cover several species of the parasite. The development of resistance is one more hurdle to cross. Despite this, scientists have picked up the gene sequence which does not change with mutation and have made the vaccine work at the laboratory level for both plasmodium vivax and falciparum. Scientists of the US Naval Medical Research Team in Djakarta [11] have independently established the development of antibodies to the circumsporozoite protein, which are important in reducing the prevalence of malaria with increasing age among persons in areas in which malaria is endemic, and have shown that the vaccine-elicited antibody to the circumsporozoite repeat region does indeed protect against infection with *P. falciparum* sporozoites.

The most advanced vaccine candidate to date is the RTS,S, which has shown a promising safety and tolerability profile in infants and is the first „proof of concept" of a malaria vaccine. In African infants the vaccine shows protection against malaria. The vaccine has gone through the Phase I and Phase II trials, and the Pivotal Phase III evaluation was started in May 2009. The most recent results were published in the New England journal of Medicine on 11 October 2011 [14]. The largest study yet of its effectiveness found it cut cases of malaria by half in children aged between five months and 17 months. Interim results from the study — which is still under way and involves more than 15,000 babies and children in seven African nations — found the vaccine cut all episodes of malaria by 55%, and cases of severe malaria by 35%. According to Jo Cohen (co-inventor of RTS,S from GlaxoSmithKline), the first broad implementation of vaccine might be possible in 2015–2016 [15].

SEAFARERS AND SEAFARING

Cases of imported malaria acquired by international travel and trade are increasingly reported. The mean annual incidence of imported malaria in Europe only reaches a level of ca. 12,000 cases. Travel has contributed to the global spread of malaria throughout the history of humankind. Travellers, and notably seafarers, visiting malaria risk areas should be properly advised on personal protective measures and chemoprophylaxis. It is probably not practical or appropriate for crew members in tropical regions to remain on malaria prophylaxis continuously, but judicious use of prophylaxis when the risk is greatest is probably the most effective way of minimizing the chances of acquiring malaria for merchant seamen. This is the thinking behind this strategy, to provide a policy in the form of guidance for intermittent prophylaxis when there is sufficient risk of malaria. It recommends a limited number of prophylactic drugs for simplicity and greatest efficacy. Both Malarone and doxycycline are well tolerated and generally safe. Use Malarone first. Doxycycline may be used as an alternative if intolerant to Malarone. The guidelines below are adapted from the existing [5] recommendations developed for seafarers by a UK based company. Ours below are divided into three sections: Section 1 deals with the prevention and treatment principles, Section 2 categorizes the risk, and Section 3 outlines the prophylactic and treatment measures, depending on geographical areas of travel. Those most likely to benefit from this strategy are the seafarers themselves, maritime doctors, ship operators, and port agents. Responsibility for knowledge and adherence to current preventative and treatment options lies with the latter two and to a lesser degree with the seafarer. The ship must be compliant with the relevant ILO/IMO and port safety codes. The Master of the ship is responsible for drawing up a recommendation for shore visits, the wearing of protective clothing, use of mosquito repellents, closing of doors and windows pre dusk, reporting of fever, lethargy, etc., and location on vessel in evenings when

in port. In addition, the Master of the vessel must also issue other deterrents for non-compliance.

PROTOCOL FOR THE AVOIDANCE, PROPHYLAXIS, AND TREATMENT OF MALARIA ON BOARD SHIP

How to use this recommendatory manual:

1. Ensure that those working in malarial areas and those responsible for their care are aware of the steps that need to be taken to prevent and treat malaria (Section 1).
2. Look up [port] on the list which is region-wise and check the risk of malaria — Category 0, 1, 2, 3 (Section 2).
3. Follow instructions on prophylaxis and treatment (Section 3).

SECTION 1: PREVENTION AND TREATMENT PRINCIPLES

The key to malaria control in crew members is:

1. Avoidance of mosquito bites
2. Appropriate prophylaxis
3. Diagnose early in unwell crew
4. Treat

1. Avoidance of malaria: Requires **A, B, C, and D**

- **A**wareness of risk
- **B**ite avoidance
- **C**hemoprophylaxis (taking preventive medicines if you are travelling to or living in a malaria region)
- **D**iagnosis made promptly with early treatment of an infected case

An **E** can be considered for seafarers in medium- and low-risk areas and those on remote adventure trips. The **E** stands for "**E**mergency treatment with safe drugs", such as Artemesin combined with Lumefantrine [8].

Living and working accommodation onboard which is sealed and air-conditioned will be safe from malaria if mosquitoes are kept out. Consider spraying rooms and cabins with pyrethroid insecticides if doors and windows have been left open for significant periods particularly at dusk when in ports where there is a high risk of malaria (West and East Africa, parts of SE Asia).

Working on deck or being on shore will increase the risk of acquiring malaria. Long-sleeved clothing, long trousers, and socks should be worn out of doors after sunset. Light colours are less attractive to mosquitoes. Insect repellents containing over 30% DEET will repel mosquitoes effectively and should be applied to exposed skin. Impregnating cotton garments with 30 ml of DEET in 250 ml of water makes them repellent. Refined lemon eucalyptus oil on skin also repels mosquitoes [15, 16].

When ashore sleep in rooms that are properly screened, with close fitting gauze over windows and doors, no holes in the gauze, and no unscreened entry points. Spray the room with a knockdown insecticide ca. one hour before evening to kill any mosquitoes that may have entered the room during the day. When sleeping outdoors or in an unscreened room, use mosquito nets around the bed at night, checking that there are no holes in the net. The net should be impregnated with pyrethroids, such as permethrin 0.2 g/m^2 of material every six months, and the net should be long enough to fall to the floor all round the bed or be tucked under the mattress. Synthetic pyrethroids should be vaporised overnight, using an electrically heated mat. Alternatively, mosquito coils (slow burning mixture of repellent and insecticide) may be burned. Electronic buzzers are sometimes marketed as repellents, but they are not effective [16].

SECTION 2: [PORTS] AND THEIR RISKS

[Ports] and specific recommendations

Check risk category level (0, 1, 2, or 3) on port list and follow the specific recommendations below.

Category 3: High-risk areas — substantial risk of acquiring malaria

Areas	East Africa south to Mozambique, West Africa south to Namibia, Oceania (PNG), NE South America, SE Asia
Avoidance	Follow policy above
Prophylaxis for crew on board	All crew members to take Malarone for one day before arrival in port, for the duration of docking, and for 7 days after leaving port
Prophylaxis for crew on shore	All shore-based crew to take Malarone for one day before arrival on shore, for the duration of shore visit, and 7 days after leaving port. An alternative is doxycycline for 2 days before shore visit, the duration of visit, and 4 weeks after leaving

Category 2: Moderate-risk areas

Areas	India, Horn of Africa, Tropical South America, Central America, Indian Ocean Islands, Remote parts of Oman (Muscat itself is malaria-free), parts of Saudi Arabia, Yemen, Iran, and Afghanistan
Avoidance	Follow policy above
Prophylaxis for crew on board	No specific prophylaxis required. Avoid mosquito bites
Prophylaxis for crew on shore	All shore-based crew to take Malarone for one day before arrival on shore, for the duration of shore visit, and 7 days after leaving port. An alternative is doxycycline for 2 days before shore visit, the duration of visit, and 4 weeks after leaving

Category 1: Low-risk areas

Areas	North Africa, Arabia, Eastwards along the coast from Antalya to the Syrian border and inland in southeast Turkey, and in parts of Syria and Iraq. South Africa (ports are safe)
Avoidance	Follow policy above
Prophylaxis for crew on board	No specific prophylaxis required. Avoid mosquito bites
Prophylaxis for crew on shore	No specific prophylaxis required. Avoid mosquito bites. If travelling for prolonged periods inland, further advice may need to be taken from a travel health expert. If in doubt, take malaria prophylaxis — Malarone or doxycycline for duration of visit as above

Category 0: Malaria NOT a risk

Areas	Europe, North America, Australia, New Zealand, southern S. America
Avoidance	Not necessary
Prophylaxis for crew on board	No prophylaxis required
Prophylaxis for crew on shore	No prophylaxis required

SECTION 3: MEDICATION FOR PROPHYLAXIS AND TREATMENT

Prophylaxis

It is probably not practical or appropriate for crew members in tropical regions to remain on malaria prophylaxis continuously, but use of appropriate prophylaxis when the risk is greatest is probably the most effective way of minimizing the chances of acquiring malaria for merchant seamen. The purpose of this policy is to provide guidance for intermittent prophylaxis when there is sufficient risk of malaria. It recommends a limited number of prophylactic drugs for simplicity and greatest efficacy. Both Malarone and doxycycline are well tolerated and generally safe. Use Malarone first. Doxycycline may be used as an alternative if a person is intolerant to Malarone [8].

Other agents which can be used are described in the text below [15] and include:

- Proguanil plus chloroquine
- Mefloquine (Lariam)
- Dapsone/Pyrimethamine (Maloprim)

Atovaquone/proguanil (Malarone)

Dose: One tablet daily — start day before entering malarious area and continue for one week after leaving.

This fixed combination of atovaquone 250 mg with proguanil 100 mg has been an effective treatment for highly chloroquine-resistant falciparum malaria for some years. Some apparent failures of prophylaxis have been recorded, but it is unclear whether they involve actual resistance to atovaquone/proguanil. One tablet daily is taken for prophylaxis. The side-effect profile appears comparable with that of the other antimalarials, as listed above, but serious adverse effects appear rare. The drug is expensive, but the reduced period of prophylaxis (one week post exposure) means that the overall cost is similar to that of mefloquine for short visits to malarious areas, as would be seen with seafarers.

Doxycycline

Dose: One tablet (100 mg) starting one week before entering malarious area and continuing for 4 weeks after leaving.

An antibiotic of the tetracycline group is active against falciparum malaria but offers limited pro-

tection against *P. vivax*. It, or atovaquone/proguanil, are the drugs of first choice for prophylaxis in areas of mefloquine-resistant malaria in Southeast Asia, and are alternative drugs to mefloquine for people visiting highly chloroquine-resistant areas, which are along the coasts of Africa, South America, India, and some parts of South East Asia. Photosensitivity may be a problem in some people. Exfoliative dermatitis has been reported but is rare. Excessive exposure to sun should be avoided by people on tropical seaside holidays, but effective sunscreens are now widely available. Doxycycline may cause diarrhoea but also may protect against some bacterial causes of travellers' diarrhoea. People using doxycycline should be warned against exposure to too much sunlight. Doxycycline should not be given to anyone with a history of allergy to tetracycline. Oesophagitis (heartburn) may result from taking the capsule on an empty stomach and/or lying down too soon after taking it. Compliance with the daily dose regimen appears to be particularly important with doxycycline.

Standby treatment

1. If malaria is expected based on:
   a. Exposure to malaria having been in a malarious area;
   b. Fever > 38°C, in paroxysms, often with flu-like symptoms of muscle aches, headaches.
2. Check diagnosis by doing finger prick blood test using the malaria test kit, following the product instructions carefully. If no kit is available on board, then treat empirically for malaria, if the above symptoms and relevant geographical history are present. It is advisable to make blood slides (thick and thin blood slides to be examined in the nearest qualified lab).
3. Seek Radio Medical Advice if available.
4. If positive result, start anti-malarial treatment immediately with: quinine 2 tablets 3 times a day for 3 days, plus one tablet of doxycycline twice daily for 7 days.
   Other standby treatments are available.

Standby treatment table 1 from [15]

CONCLUSIONS

Human infection with *Plasmodium* species leading to clinical episodes of malaria probably began very early in the history of humankind and has persistently inflicted disease among human populations. Malaria is currently considered the world's most important parasitic infection. The global impact of malaria is incalculable and appears to have increased over the past few decades. Most of this burden of disease is carried by developing tropical countries. These numbers are growing because of increased travel to malaria-endemic areas and also due to increased risk of transmission in these areas. Non-adherence to chemoprophylactic regimens is frequently secondary to drug side effects. Therefore, a careful risk-benefit analysis on the use of anti-malarial prophylaxis should be carried out in every individual travelling to malaria risk areas. Standby malaria self-treatment is not an alternative in seafarers travelling to relatively low-risk areas. The goal of the above recommendation is to be simple yet practical and to provide a resource for the seafaring community, especially medical physicians seeking Malaria information. It thereby strives to address the main issues of

Table 1. Standby treatment table from reference [9]

Situation for use	Standby treatment regimen	Usual amount per tablet	Adult dose
Multidrug-resistant falciparum malaria	Atovaquone-proguanil (*Malarone*)	250 mg plus 100 mg	4 tablets as a single dose on each of three consecutive days
Multidrug-resistant falciparum malaria	Co-artemether (*Riamet*)	20 mg artemether plus 120 mg lumefantrine	6 doses of 4 tablets over a period of 60 hours
Multidrug-resistant falciparum malaria	Quinine plus doxycycline	200 mg quinine and 100 mg doxycycline	Quinine 2 tablets 3 times a day for 3 days, accompanied by 1 tablet of doxycycline twice daily for 7 days
Recommended where no chloroquine resistance present	Chloroqiune (*Nivaquine/Avloclor*)	150 mg chloroquine base (*Nivaquine*) or 155 mg chloroquine base (*Avloclor*)	4 tablets on days 1 and 2, 2 tablets on day 3
Pregnancy	Quinine	300 mg quinine	Quinine 2 tablets 3 times a day for 5–7 days

malaria and reduce the morbidity and to a lesser extent the mortality, in seafarers. The IMHA as an International Maritime Health Advisory Body can assist the stakeholders upon requests or advice for developing specific Malaria Protocols.

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